Scientists identify novel compound to alleviate pain and itch

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Professor Laura Bohn led the study on the Florida campus of The Scripps Research Institute. Credit: James McEntee

In a new study, scientists from the Florida campus of The Scripps Research Institute (TSRI) have identified a possible drug candidate that suppresses pain and itch in animal models. Their new approach also reduces the potential for drug abuse and avoids the most common side effects—sedation and anxiety—of drugs designed to target the nervous system's kappa opioid receptors (KORs).

"The most significant aspect of the study is that we can preserve itch and pain treatment qualities in a KOR agonist that we developed—triazole 1.1—while avoiding the euphoria associated with narcotic opioids and the dysphoria associated with some other selective KOR agonists," said TSRI Professor Laura Bohn, senior author of the new study.

The research was published this week online ahead of print in the journal *Science Signaling*.

Circumventing Side Effects

KORs help regulate the release of the neurotransmitter dopamine. Drugs that target KORs have shown promise as therapeutic candidates because of their efficacy for treating chronic itch and relieving pain. Unlike opioid narcotics that target other opioid receptors, these compounds do not produce a "high" or increased risk of overdose; however, they can deplete the body's supply of dopamine and produce dysphoria and sedation, side effects that have limited their clinical development.

Bohn's laboratory has pioneered the concept that KOR signaling can be fine-tuned to preferentially activate certain pathways over others so that the receptor signals through G proteins rather than through a protein called ?-arrestin2.

In the new study, the researchers used rodent models to compare this kind of "biased" KOR agonist, called triazole 1.1, and a conventional KOR agonist.

They found that triazole 1.1 could indeed circumvent the two side effects of previously developed KOR compounds without decreasing dopamine levels, a property associated with dysphoria and sedation.

"This adds to the mounting evidence that shows analgesic effects can be separated from the sedative and dysphoric effects by altering how the agonist engages the receptor," said TSRI Research Associate Tarsis Brust, first author of the study.

Bohn said the new findings clearly demonstrate that the strategy of developing biased KOR agonists offers a promising new way to treat pain and intractable itch without the potential for abuse.

More information: T. F. Brust et al, Biased agonists of the kappa opioid receptor suppress pain

and itch without causing sedation or dysphoria,
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